below) and hence both CS193 and CS194, which are part of the pathway downstream of GCC, have considerable value as colon specific markers.

Specifically, GCC is a member of the family of receptor guanylyl cyclases, of which six members have been identified in mammals. Guanylyl cyclases represent complete signal transducing units that do not require additional components. They combine the components of s signal receptor, a signal transducer and an enzymatic effector (Fulle, H-J. and D. L. Garbers (1994) Guanylyl Cyclases: a Family of Receptor-Linked Enzymes. *Cell Biochem. and Function.* **12**, 157-165). Peptides that specifically bind to GCC include the *E. coli* heat-stable enterotoxin, guanylin, and uroguanylin. Ligand binding to GCC activates guanlyly cyclase and elevates intracellular cGMP, resulting in phosphorylation of the cystic fibrosis transmembrane conductance regulator, increases in chloride flux, and, ultimately, fluid secretion (Carrithers, S. L., *et al.,* (1996) Guanylyl cyclase C is a Selective Marker for Metastatic Colorectal Tumors in Human Extraintestinal Tissues. *Proc. Natl. Acas. Sci. USA.* **93**, 14827-14832). In humans, GCC is expressed by mucosal cells lining the intestine, from the duodenum to the rectum, but not in any other extraintestinal tissue making it a highly tissue specific marker for colorectal cancer (Waldman, S. A., *et al.,* (1998) Use of Guanylyl Cyclase C for Detecting Micrometastases in Lymph Nodes of Patients with Colon Cancer. *Dis. Colon Rectum* **41**(3), 310-315). GCC persists after intestinal mucosal cells undergo neoplastic transformation, allowing it to be identified in all primary and metastatic colorectal cancers. The utility of GCC as a biomarker for colorectal cancer includes diagnosing, staging, and postoperative monitoring of patients (Cagir, B. *et al.,* (1999) Guanylyl Cyclase C Messenger RNA is a Biomarker for Recurrent Stage II Colorectal Cancer. *Ann. Intern. Med.* **131**(11), 805-812; Waldman*et al.*,1998, *supra*;). Thus, it is evident that CS 194 has a definite link to cancer and makes it an excellent cancer marker when used to detect tumor growth in the digestive tract.

In addition, CS194 has high tissue specificity. CS194 is a previously unknown polynucleotide that codes for a protein 914 amino acid long and is useful as a diagnostic marker for diseases of the Gastrointestinal tract (GI) due to its abundance in GI tract tissue.

Based on quantitative analysis of the occurrence of the CS194 polynucleotide in human GI tissue samples compared to human tissue samples representing the body as a whole, CS194 is approximately **104** times more abundant in GI tissue than in the rest of

the body. {Data are obtained from the Lifeseq database developed by Incyte Pharmaceuticals.} As is known scientists skilled in the cancer diagnostic arts, a gene product, such as a protein or messenger RNA (mRNA) coding for the protein, which is more prevalent and highly specific to one tissue type than other tissue types, is extremely useful as a marker for the detection of disease in that tissue. If a protein appears in a tissue or body compartment where its normal occurrence is very low or non-existent, then the specific tissue in which the protein is normally found is in a diseased state. This is because the disease causes an alteration to the protein-specific tissue resulting in the protein escaping from its normal tissue into another. There are three main conditions which cause a tissue-specific protein to exist outside its specific host tissue: massive trauma, ischemia and hypertrophic proliferation. Thus, if a patient has not experienced a massive trauma or ischemia, detection of a tissue-specific protein outside that protein's host tissue indicates that the precise disease is hypertrophic proliferation of that tissue, the most serious form being cancer. There are many examples of the diagnostic use of tissue-specific protein markers. For instance, the appearance of prostate specific antigen (PSA) in seminal plasma is normal, but its detection in blood is indicative of prostate cancer. Further, the appearance of PSA messenger RNA (mRNA) in blood is indicative of prostate cancer. Likewise, the appearance of carcinoembryonic antigen (CEA) in colon and stool is normal, but its detection in blood at elevated levels is indicative of colorectal cancer. The attached Exhibit A illustrates the usefulness of tissue specific molecules which, upon detection in circulation, indicate proliferative disease. For Example, Exhibit A states that CEA is expressed in normal adult tissue but is detected in serum in patients with colorectal and other carcinomas. (p. 67, col. 2):

> *Some years after the discovery the same research group found that CEA could be measured in serum from patients with colorectal cancer and other carcinomas....[s]era from healthy individuals and from patients with other diseases generally had low levels of CEA... CEA assays are now generally accepted as a useful and cost-efficient tool in monitoring colon cancer...*

This journal article explains how a tissue specific molecule, expressed in the colon in normal individuals, is drained into lymph and blood vessels upon colon tumor growth. (Fig. 5)

In addition, the attached Declaration of Dr. Paula Friedman further proves the importance and usefulness of tissue-specific markers, such as CS194. In her Declaration, Dr. Friedman illustrates the similarities between well-known markers CEA and PSA and the novel CS194 when analyzed using the Incyte database. As shown, the tissue specificity of CS194 closely resembles the tissue specificity of the above mentioned cancer markers. Clearly, the presence of CS194 outside of the GI tract illustrates cancer development of that tissue, just as the presence of CEA and PSA outside of their respective tissues indicates cancer of the colon and prostate, respectively. Thus, the above scientific facts support the utility of CS194 and illustrate that the appearance of CS 194 protein or mRNA in a patient blood sample is indicative of GI tract disease in that patient.

Thus, the above scientific facts support the utility of CS194 and illustrate that the appearance of CS194 protein or mRNA in a patient blood sample is indicative of GI tract disease in that patient.

The Examiner is reminded of the proper standard under the Revised Interim Utility Guidelines which specifically states that utility is acceptable if it is "believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided". The Guidelines continue stating "[A]n assertion is credible unless (a) the logic underlying the assertion is **seriously** flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion", (emphasis added). Simply put, the threshold to be met by Applicant is a **credible assertion** of utility, not the extraordinarily high threshold improperly held by the Examiner. Clearly, the appearance of a secreted CS194 gene product outside the GI tissue itself, such as in whole blood, urine, stool or serum, indicates a form of GI tract disease, akin to the presence of common markers such as PSA and CEA found in blood outside of their prevalent tissue type. CS194's use in diagnostic test in order to determine whether a patient has a disease of the GI tract unquestionably illustrates a credible utility.

Therefore, it is requested that this rejection be withdrawn.

Claims 1-6, 11, 15, 17, and 18 are also rejected under 35 U.S.C, §112, first paragraph. For example, the claims are directed to purified polynucleotides selected from the group consisting of polynucleotides have 50% identity to SEQ ID NOS. 1-8, 10-12,

15-20, and polynucleotides having 70% identity to SEQ ID NOS. 9, 13 and 14, or complements thereof.

Further, with regard to claims 17 and 18, directed to genes, the Examiner states that in view of the fact that the art does not provide an accepted definition for the term "gene", an elaboration of its characteristics (i.e., sequence) would require both a disclosure of a definition for the term and a characterization of the sequence thereof.

Applicant has raised the percent identity to 95% and amended claims 17 and 18 to omit "gene" and substitute "isolated polynucleotide" therefor. Therefore, it is requested that this rejection be withdrawn.

Claims 1-6, 11, 15, 17, and 18 are rejected under 35 U.S.C. §112, first paragraph. The Examiner states that the claims are directed to purified polynucleotides selected from the group consisting of polynucleotides having 50% identity to SEQ ID NOS. 1-8, 10-12, 15-20, and polynucleotides having 70% identity to SEQ ID NOS. 9, 13, and 14, or complements thereof.

Applicant has raised the percent identity to 95% and amended claims 17 and 18 to omit "gene" and substitute "isolated polynucleotide" therefor. Therefore, it is requested that this rejection be withdrawn.

The Examiner further states that the specification does not teach a specific algorithm or parameters required to calculate the claimed sequence identity, such as, the necessary parameters required to calculate the claimed sequence identity, using a disclosed, given algorithm, include gap penalties and mismatch penalties.

The Examiner is reminded that Applicant submitted the Wisconsin Sequence Analysis Program, Version 8, software manual in the Response dated April 5, 2000. This software program is referred to in the specification on page 11, starting on line 2. This publically available document is well known to those in the art and explains the calculation of percent identity, including the appropriate algorithms and penalties.

Thus it is requested that this rejection be withdrawn.

With regard to claims 4 and 11, the Examiner states that the claims are not enabled for polynucleotides encoding an epitope wherein the polynucleotides are selected from polynucleotides having 50% identity to SEQ ID NOS. 1-8, 10-12, 15-20 and

polynucleotides having 70% identity to SEQ ID NOS. 9, 13, and 14 or complements thereof.

Based on the amendments which raise percent identity significantly and applicant's arguments made April 5, 2000, it is respectfully requested that this rejection be withdrawn.

Claim 18 remains rejected under 35 U.S.C. §102(b) as being anticipated by Cunningham et al. (J. Biol. Chem., 270:52, 31016-31026, 1995) for the reasons of record.

Applicant has raised the percent identity significantly in Claim 18, thereby removing the prior art reference.

CONCLUSION

In view of the aforementioned amendments and remarks, the aforementioned application is in condition for allowance and Applicant requests that the Examiner withdraw all outstanding objections and rejections and to pass this application to allowance.

Respectfully submitted,

P. A. Billing-Medel, *et al.*

Abbott Laboratories
D377/AP6D-2
100 Abbott Park Road
Abbott Park, IL 60064-6050
(847) 935-7550
Fax: (847) 938-2623

Mimi C. Goller
Registration No. 39,046
Attorney for Applicants